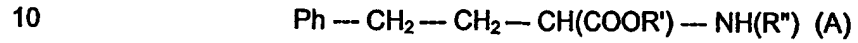
STEREOSELECTIVE SYNTHESIS OF 2-HYDROXY-4-PHENYLBUTYRIC ACID ESTERS

The present invention relates to a process for the synthesis of chiral compounds, and in particular chiral esters, for use as intermediates in the synthesis of the family of acetylcholine esterase (ACE) inhibitors known as 'prils'.

The 'prils' have the general formula (A):



$$Ph - CH_2 - CH_2 - CH(COOR') - NH(R'') \quad (A)$$

wherein R' is hydrogen or C_1-C_2 alkyl and R" is selected from a large number of possible moieties. Examples of 'prils' include lisinopril, cilazapril, enalapril, benazepril, ramipril, delapril, enalaprilat, imidapril, spirapril, trandolapril and others.

These 'pril' compounds are chiral compounds, only one of their diastereomers being pharmacologically active. It is therefore necessary to isolate and purify the active diastereomer, rather using a racemic mixture, for pharmaceutical/medical applications.

Typically, separation of diastereomers is carried out by preferential crystallisation, for example as described in US patent specification no. 5,616,727. However, the yields of such crystallisations are often low and, indeed, the yield from the process used in US patent specification no. 5,616,727 was only 68%.

Alternatively, a stereochemical synthesis may be used, wherein various intermediates used in the preparation of the 'prils' are, in turn, prepared in chiral form, which results in a predominance of the desired diastereomer in the final 'pril' product. However, such chiral syntheses are complex and the yields are also unsatisfactory.

The present invention relates to an improved, stereospecific process for the synthesis of an intermediate for making 'pril' compounds. This intermediate can be converted to the required 'pril' isomer, or any other desired end-product, without loss of stereospecificity. The intermediate of interest is an ester of formula (I):

$$Ph — CH_2 — CH_2 — CH(OR^2)^* — COOR^1 \qquad (I)$$

wherein * signifies the (R) stereoisomer;
R^1 is selected from C_{1-6} alkyl, preferably ethyl; and
R^2 is hydrogen, a protecting group or a leaving group.

Suitable leaving groups R^2 include p-toluene sulphonyl (tosyl), methane sulphonyl chloride (mesyl), trifluoromethane sulphonyl (triflic), and p-nitrobenzene sulphonyl.

Suitable protecting groups R^2 include *tert*-butyl dimethyl siliyl (TBDMS), TMS, BOC and the like.

One method of stereospecific synthesis involves the conversion of the compound (R)-2-hydroxy-4-phenylbutyronitrile having the formula (II):

$$Ph — CH_2 — CH_2 — CH(OH)^* — CN \qquad (II)$$

wherein * signifies the (R) stereoisomer; and Ph is the phenyl group $C_6 H_5$ to the corresponding ester of formula (I).

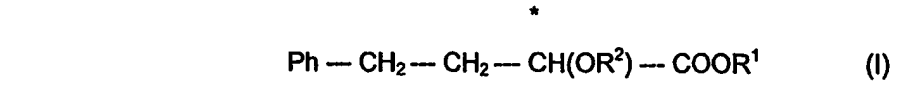
In Tet. Lets. 30 (15) 1917-20 (1989) is disclosed the above process to produce a compound of formula (I) wherein R^2 is H and R^1 is ethyl. However, the method described involves a three-stage process, resulting in a yield of only 78%, based on the nitrile of formula (II). The three process steps are: (i) treating the nitrile (II) with dihydopyran *in pyridinium p-toluene sulphonate to prepare the* THP derivative; (ii) hydrolysing the nitrile group with sodium hydroxide; and, finally, treating the resulting acid with anhydrous ethanol and a catalytic amount of concentrated sulphuric acid.

We have therefore looked at the possibility of using alternative methods of synthesising this ester, but none of these appeared to provide the desired combination of high *ee* (*eg* 97-98%); conomic reaction time; acceptable yields (*eg* > 80%); and overall ease of handling and commercial viability of the proc ss.

Instead, we have surprisingly found that, by careful selection of novel reaction conditions and reagents, we can obtain the desired *ee* in high yields and under commercially-acceptable conditions, involving a so-called 'one-pot' reaction, in which the reaction appears to go in one step, without the addition of further reagents or reactants, but with the formation of an unstable intermediate that need not be isolated but converts *in situ* to the desired compound of formula (I).

The novel one-pot reaction according to this invention involves reacting the nitrile of formula (II) with an alcoholic solution of an inorganic acid, such as sulphuric acid or hydrochloric acid, to give the ester of formula (I) *via* an *in situ* conversion.

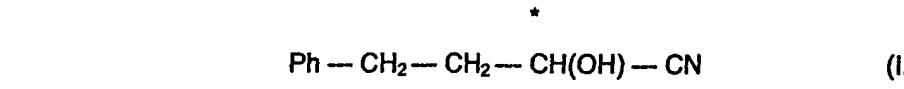
There is therefore provided a process for the stereospecific preparation of an ester of formula (I):



$$Ph - CH_2 - CH_2 - CH(OR^2) - COOR^1 \qquad (I)$$

wherein * signifies the (R) stereoisomer;
R^1 is selected from C_{1-6} alkyl, preferably ethyl; and
R^2 is hydrogen, a protecting group or a leaving group

which process comprises reaction of a nitrile of formula (II):



$$Ph - CH_2 - CH_2 - CH(OH) - CN \qquad (II)$$

wherein * signifies the (R) stereoisomer; and Ph is the phenyl group C_6H_5
with a solution of an inorganic acid in an alcohol
and optional conversion of the compound of formula (I) wherein R^2 is H so prepared to any other desired compound of formula (I) by standard methods known to those skilled in the art.

Accordingly, the present invention further provides a process for preparing a compound of formula (I), which process comprises reaction of an intermediate imine of formula (III):

$$[Ph — CH_2 — CH_2 — CH(OR^2) — CH{=}NH.HX] \qquad (III)$$

in which R^2 is as defined in formula (I); and X is the anion of an inorganic acid, such as sulphate or halide, preferably halide, more preferably chloride, with an alcohol of formula R^1OH, in which R^1 is as defined in formula (I).

It is preferred that R^1 is C_1-C_4 alkyl, for example methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *iso*-butyl or *tert*-butyl. Accordingly, ethanol is the preferred alcohol. Conveniently, the alcoholic solution of the acid is prepared by bubbling dry, gaseous acid into absolute alcohol. Preferable, the solution comprises at least 4-5% w/v of acid (gas), more preferably > 7%w/v, such as in the range of from 7-15% w/v, based on grams of acid per 100ml of alcohol.

It is preferred that the alcohol/acid solution be as anhydrous as possible, in order to ensure that the ester is formed in preference to the corresponding acid. The reaction may be carried out at a temperature in the range of from 0 to 80 °C, such as at reflux temperature of the reaction mixture, at atmospheric pressure. For example, using the ethanol/HCl, the reaction may be carried out at 70-85 °C over a period in the range of from 12 to 20 hours, such as at 75-80°C over a period of 15 hours, or for 2 hours at 10-15 °C followed by refluxing for 15 hours, all at atmospheric pressure. The skilled chemist will be able to adjust the temperature/pressure/reaction period factors appropriately.

The ratio of nitrile of formula (II): acid/alcohol solution is in the range of from 1:6 to 1:10, preferably about 1:8, by volume.

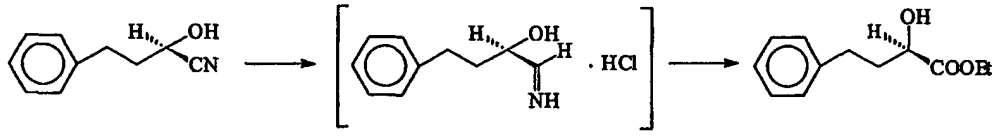
The yield of this reaction is about 80% of theoretical with an enantiomeric excess (*ee*), based on optical rotation, of the (R) isomer of about 97%.

The present invention therefore further provides an ester of formula (I), in particular, an ester of formula (I) comprising at least 97% of the (R) isomer, whenever prepared by a process according to this invention; and such a compound (I) for use in, or whenever used in, the preparation of a stereospecific 'pril' of formula (A).

Furthermore, there is provided a method for the preparation of a stereospecific 'pril' of formula (A), which method comprises preparation of an ester of formula (I) by a process according to this invention; and a stereospecific 'pril' of formula (A), whenever prepared by such a process.

The invention will now be described in more detail with reference to the following non-limiting examples.

Exampl : Pr parati n of (R)-2-Hydroxy-4-phenyl butyric acid



(R)-isomer (R)-isomer

(II) (III) (I)

(a) Preparation of alcoholic HCl (g)

To 1 kg of common salt (NaCl) was added 250 ml of concentrated sulphuric acid, dropwise at room temperature. The hydrogen chloride gas evolved was first passed through a trap containing concentrated sulphuric acid to dry it and then passed with stirring into absolute alcohol (2l) which was kept at 0-5°C. The process was carried out for 4-6 hours until the required strength was obtained.

(b) Preparation of Title Compound

To (R)-2-hydroxy-4-phenyl-butyronitrile ((II), 250g, 1.55 M) was added absolute alcohol (2l) which contained at least 7% w/v of dry hydrogen chloride gas at 10-15°C. The mixture was stirred for 2 hours at the same temperature. This was carried out to allow confirmation of the conversion of the nitrile to the corresponding imine hydrochloride. After this, the reaction mass was refluxed at 75-80°C. The reaction was monitored using TLC and after 15 hours was found to be complete.

The alcohol was removed from the reaction mass *in vacuo* at 55-60°C. The resulting residue was taken in water (1l) and extracted with dichloromethane (500 ml x 2). The collective organic phases were dried over anhydrous sodium sulphate and concentrated *in vacuo* to yield a reddish, thick liquid. This was vacuum-distilled to obtain the desired product in 78-80% yield (of theoretical), as a colourless liquid.

The whole process can be summarized as follows :

Substrate	Substrate in Ethanolic HCl	HCl concentration	T mp	Tim	Yield	Purity by HPLC
(R)-2-Hydroxy-4-phenylbutyronitrile	1 : 8 by volume	7-15% w/v	75-80°C	15 hrs	78-80% of theoretical	98%

Analytical data :

$^{20}[\alpha]_D$: -10 at 100% concentration (solvent free).

Reported $^{20}[\alpha]_D$: -10 ± 1 at 100% concentration (solvent free).

Boiling point: 125-127°C at 1mm Hg to 2 mm Hg vacuum; 120°C at 1.5 mm

NMR (Varian^{RTM} 60 MHz): (CCl_4, TMS) 7.3 (S, 5 H), 3.8-4.3 (m, 3 H), 2.5 – 2.8 (t, 3 H), 1.4-2 (m, 2 H), 1-1.3 (t, 3 H)

Density: 1.0751

Refractive index: 1.502

HPLC 1: Column C_{18} (250 mm X 4.6 mm X 5 μ); mobile phase: methanol : H_2O (80 : 20); wavelength: 210 nm; flow rate: 1 ml/min; retention time: 4.17 minutes

HPLC 2: Column C_{10} Si 60 (5 μm) (250 mm X 4.0 mm X 5 μ); mobile phase: hexane : ethyl acetate (90 : 10); wavelength: 254 nm; flow rate: 1.0 ml/min; retention time: 21.60 minutes

IR: OH 3400 cm^{-1} – 3500 cm^{-1}; C=O 1750 cm^{-1}

All publications, patents, and patent documents, cited in this application, are incorporated by reference herein, as though individually incorporated by reference. In the case of any inconsistencies, the present disclosure, including any definitions therein, will prevail.

The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.